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Hibernation constrains brain size evolution in mammals

Abstract

The expensive brain hypothesis predicts that the lowest stable level of steady energy input acts as a strong constraint on a species' brain size, and thus that periodic troughs in net energy intake should select for reduced brain size relative to body mass. Here, we test this prediction for the extreme case of hibernation. Hibernators drastically reduce food intake for up to several months, and are therefore expected to have smaller relative brain sizes than non-hibernating species. Using a comparative phylogenetic approach on brain size estimates of 1104 mammalian species, and controlling for possible confounding variables, we indeed found that the presence of hibernation in mammals is correlated with decreased relative brain size. This result adds to recent comparative work across mammals and amphibians supporting the idea that environmental seasonality (where *in extremis* hibernation is necessary for survival) imposes an energetic challenge, and thus acts as an evolutionary constraint on relative brain size.

Keywords: seasonality, brain size evolution, hibernation, heterothermy, over-wintering, energy savings

Introduction

Relative brain size shows massive variation across mammalian species (e.g., Striedter, 2005). Large brains are presumed to have been favoured by natural selection because they provide a wide range of benefits in both the social (e.g., Byrne & Whiten, 1988; Barrett & Henzi, 2005; Emery *et al.*, 2007; Dunbar & Shultz, 2017) and ecological domain (e.g., Parker & Gibson, 1977; Sol, 2009; Benson-Amram *et al.*, 2016; Heldstab *et al.*, 2016a; Heldstab *et al.*, 2016b; Navarrete *et al.*, 2016; Powell *et al.*, 2017). But these multifaceted benefits conferred by a

large brain are counterbalanced by the higher energetic demands of larger brains. Brain tissue is among the most metabolically costly tissues in the body to maintain (Niven & Laughlin, 2008). For instance, humans shunt about 20-25% of all metabolic energy at resting state to a brain that constitutes only 2% of their body mass, and costs are also considerable for other animals (Mink *et al.*, 1981). Furthermore, brains need a constant supply of energy at all times (Mink *et al.*, 1981; Lukas & Campbell, 2000). Not only brain maintenance but also brain growth is energetically very expensive (Bauernfeind *et al.*, 2014; Kuzawa *et al.*, 2014). As a result, larger-brained species develop more slowly (Sol *et al.*, 2007; Isler & van Schaik, 2009; Barton & Capellini, 2011; Yu *et al.*, 2018) and thus reach adulthood later - a considerable fitness cost. Thus, for a species to evolve a relatively larger brain than its ancestor, the fitness benefits of having a larger brain have to outweigh these high costs of brain development and maintenance.

While the majority of previous studies focused on the benefits of increased brain size, the expensive brain hypothesis (Isler & van Schaik, 2009) emphasizes its costs. It postulates that an evolutionary brain enlargement is either constrained by the energy allocation to other functions (e.g., costly locomotion: Navarrete *et al.*, 2011; Heldstab *et al.*, 2016b) or by the total energetic input (Isler, 2011; Isler & van Schaik, 2012; Pontzer *et al.*, 2016; Genoud *et al.*, 2017; Powell *et al.*, 2017). Animals living in seasonal habitats experience periods of severe food scarcity. If they find no adequate food resources during these lean seasons, their dietary intake cannot sustain the energetic maintenance costs of a large brain relative to body mass. Unavoidable periods of starvation are therefore expected to acts as an energetic constraint on brain size. Recent comparative work across mammals (van Woerden *et al.*, 2012; van Woerden *et al.*, 2014; Weisbecker *et al.*, 2015) and amphibians (Luo *et al.*, 2017) confirms this fundamental assumption of the expensive brain hypothesis, namely that animals

with periodic troughs in energy intake are unable to maintain large brains due to the inability of brains to cope with temporary reductions in energy supply.

Such periodic troughs in energy intake reach their apogee in hibernating species, which may survive lean periods by reducing energy expenditure down to as little as 6% of the basal metabolic rate shown during activity periods (for a review, Ruf & Geiser, 2015). Due to this drastic reduction of energy input, hibernating species may not be able to hold the energy supply for a large brain constant. In this paper, we therefore test a modified prediction of the expensive brain hypothesis, namely that if the level of stable energy inputs determines a species' brain size, the presence of hibernation is expected to be correlated with decreased brain size relative to body mass. We test this prediction in a large sample of 1104 mammalian species.

Materials and Methods

Data

We compiled a broad dataset on brain and body mass, as well as hibernation for a total of 1104 mammalian species from 25 orders. Data on brain size and body mass were retrieved from established databases and from the published literature. Whenever possible, we used female values to reduce error due to sexual dimorphism. If available, body mass was taken from the same specimens as brain size. Otherwise, the largest available sample of wild body mass data was used. Following traditional classification criteria, hibernation was defined as a hypomethabolic state lasting for multiple consecutive days associated with low body temperature, profoundly reduced metabolic rate and cessation of normal foraging behaviour (for a review, Ruf & Geiser, 2015). Hibernation was coded as a binary variable with (0) for non-hibernating and (1) for hibernating species with data from the published literature. Fully aquatic taxa such as Cetacea and Sirenia were excluded from being sampled because

hibernation is fundamentally impossible for them. Detailed sources of data for the whole dataset are given in Appendix S1.

Environments with greater seasonality in temperatures and day length have been shown to select for larger body size in mammals (e.g., Ashton *et al.*, 2000; Meiri & Dayan, 2003; Plavcan *et al.*, 2005). Although hibernation occurs all across the globe from the arctic to the tropics (Lyman, 2013), it is usually the animals in seasonal habitats that hibernate (Ruf & Geiser, 2015). We therefore added mid-latitude of the species' geographical distribution as covariate in our analyses (data from Jones *et al.*, 2009; Heldstab *et al.*, 2018; IUCN, 2017).

Diet quality, activity period (relative to the daily light cycle) and predominant locomotion substrate have been shown to correlate with brain size in mammals (Harvey *et al.*, 1980; Gittleman, 1986; e.g., Bernard & Nurton, 1993; Kirk, 2006; Powell *et al.*, 2017). Although it is less clear how these variables should be related to hibernation, our large sample size allowed us to include these potentially confounding variables into our analyses. Data for these covariates were collated from the literature (detailed references in Appendix S1). To control for diet quality, species were divided into four categories based on their main diet: herbivore or folivore (1), frugivore/folivore or granivore (2), frugivore/faunivore or omnivore (3) and faunivore, piscivore, carnivore or insectivore (4). A binary coding was used for activity period, with (0) for nocturnal, cathemeral or crepuscular species and (1) for diurnal species. For substrate use, each species was assigned to one of five substrate use categories: semi-aquatic (1), fossorial or semi-fossorial (2), terrestrial or semi-arboreal (3), arboreal (4) and volant (5).

Statistical analyses

All statistical analyses were done in JMP^{TM} 13.0 (SAS Institute Inc, 1989-2016) and in R3.4.1 (R Core Team, 2017). Brain size and body mass values were $\log_e$-transformed before analysis to reduce the skew of their distribution. Because the phylogenetic signal lambda (λ)

was always close to 1, the use of methods to control for phylogenetic non-independence was warranted (Pagel, 1999). We therefore built phylogenetic generalized least-squares regression (PGLS) models (Freckleton *et al.*, 2002) using the "caper" package (Orme, 2013) in R. The phylogeny was based on a composite supertree (Fritz *et al.*, 2009). We used PGLS models with brain size as dependent variable, and hibernation, female body mass and the possible confounding variables (diet quality, diurnality, substrate use and mid-latitude of geographical distribution) as independent variables. We also tested alternative models including interaction terms between hibernation and the other predictor variables but none of these interaction effects was statistically significant, neither when tested singly nor combined in one model. Also, when polytomies were resolved in random order using the "multi2di" function from the "ape" package in R (Paradis *et al.*, 2004) to generate a fully resolved bifurcating phylogeny, the results remained largely identical (results not shown). In a second step, we performed the same analyses as mentioned above, excluding all mammalian orders with no hibernators. Lastly, to investigate the effect of hibernation on brain size in detail we also analysed all orders containing hibernating and non-hibernating species separately.

Results

As predicted by the expensive brain framework, our analysis across a comprehensive sample of over 1100 mammal species showed that hibernators have significantly smaller relative brain sizes than non-hibernating species (Table 1). We found no difference in the results when we controlled for various possible confounding variables (diet, diurnality, substrate use and mid-latitude of geographical distribution) (Table 1), suggesting that these findings are not spurious by-products of other correlations.

Results of the subset excluding all mammalian orders with no hibernators are strikingly similar (Table 1). In a more detailed analysis within orders, we consistently found in all orders that relative brain size was smaller in hibernators compared to non-hibernating species, although the difference did not reach statistical significance in Eulipotyphla and Primates (Table 2, Fig. 1; see also Table S1 for all results within orders corrected for potential confounding effects of diet, diurnality, substrate use and mid-latitude of geographical distribution).

Discussion

We found that hibernators have significantly smaller relative brain sizes than non-hibernating species covering a wide taxonomic range of 1104 mammalian species. Together with earlier findings in mammals (van Woerden *et al.*, 2012; van Woerden *et al.*, 2014; Weisbecker *et al.*, 2015) and amphibians (Luo *et al.*, 2017), our study corroborates the fundamental prediction of the expensive brain framework, namely that animals experiencing periodic troughs in energy intake, reaching its apogee in hibernating species, evolved a reduced brain size, reflecting the inability of brains to cope with temporary reductions in energy supply.

Hibernation occurs all across the globe from the arctic to the tropics which illustrates that mammals hibernate mainly to survive prolonged seasonal periods of food shortage (Lyman, 2013). During these periods of starvation, the brain is sustained by metabolising fat involving ketone bodies (Owen *et al.*, 1967; Zhang *et al.*, 2013). This can be a successful strategy to survive seasonally lean periods (e.g., Knott, 1998), but on balance it is metabolically less efficient than direct energy intake (Sokoloff, 1973; Mitchell & Fukao, 2001). Therefore, hibernators can only survive these long periods of fasting by drastically downregulating energy expenditure (for a review, Ruf & Geiser, 2015). As a result, individuals may not be able to supply a large brain with the constantly high energy flow it

needs. Consequently, selection should favour increased brain size only for species which are active throughout the year and hence benefit from using their larger brains continuously, for instance by being behaviourally more flexible in foraging behaviour and exploiting a broader diet (van Woerden *et al.*, 2012; van Woerden *et al.*, 2014; Heldstab *et al.*, 2016a; Navarrete *et al.*, 2016). The majority of hibernating species, however, spends at least one-third to one-half of their total lifetime in hibernation and is therefore expected to exhibit relatively small brains. Support for this hypothesis derives not only from the present study but also from an intraspecific study in Andrew's toads (*Bufo andrewsi*), which found that populations with longer periods of hibernation had smaller brains (Jiang *et al.*, 2015). Furthermore, a study in extant and extinct bear species reveals that brain size is smaller in species that exhibit dormancy and have a low caloric diet (Veitschegger, 2017).

An additional explanation for why we found relatively small brains in hibernating species is that the extended inactivity of brain cells and tissue during hibernation may result in adverse effects of hibernation on cognition. Hibernating European ground squirrels (*Spermophilus citellus*) showed a lower memory retention than non-hibernating individuals of the same species, and some behaviours even required relearning in the following spring after hibernation (Millesi *et al.*, 2001). A possible explanation for this memory loss might be a reduction in neuronal connectivity during hibernation as shown for Arctic ground squirrels (*Urocitellus parryii*) (Popov and Bocharova, 1992; Popov et al., 1992) and Golden-mantled ground squirrels (*Spermophilus lateralis*) (von der Ohe *et al.*, 2006). Furthermore, EEG-measurements of torpid animals have shown that almost no brain activity is present (Walker *et al.*, 1977; Krilowicz *et al.*, 1988; Daan *et al.*, 1991). The above-mentioned findings indicating negative effects of hibernation on cognition may pose important constraints on animals. For instance, large-brained species such as anthropoid primates (Isler *et al.*, 2008; Isler & van Schaik, 2012), which rely heavily on learning to solve a wide range of complex

problems, would be too much impacted by the memory loss occurring during hibernation. However, more recent studies on greater mouse-eared bats (*Myotis myotis*) (Ruczynski & Siemers, 2011) and Alpine marmots (*Marmota marmota*) (Clemens *et al.*, 2009) found no effect of hibernation on memory retention, but hibernation times may have been too short to find an effect in these studies. Future studies are therefore needed to investigate whether these negative effects of hibernation are species-specific or a general phenomenon.

Brain size was consistently smaller in hibernators compared to non-hibernating species within all orders, with two exceptions, Eulipotyphla and Primates. Overall, hibernation is a rare behaviour occurring only in around 8% of all mammalian species in our dataset. In primates, it is even rarer with roughly 2% of all primates hibernating in our sample (5 hibernators versus 200 non-hibernators). The only three primate genera known to hibernate (*Cheirogaleus*, *Microcebus*, and *Nycticebus*) (Schülke & Ostner, 2007; Ruf *et al.*, 2015) are among the smallest-brained primates (Isler *et al.*, 2008), thus, the non-significance of the result in this order is most likely due to the highly unbalanced sample. A possible explanation for the rare occurrence of hibernation in primates might be that adverse effects of hibernation such as memory loss and the impossibility of a constant high energy supply for brain maintenance are experienced as more severe in primates because in general, primates are relatively large-brained mammals (Isler *et al.*, 2008; Isler & van Schaik, 2012). Furthermore, the costs of transporting additional body fat are especially high in arboreal species such as primates, making such fat deposits and thus hibernation a less profitable strategy to survive seasonally lean periods in this order (Heldstab *et al.*, 2016b).

The other order showing no significant effect of hibernation on brain size was Eulipotyphla. Several species within this order such as the white-toothed shrew (*Crocidura russula*), the desert shrew (*Notiosorex crawfordi*) or the pygmy white-toothed shrew *(Suncus etruscus*) are known to use daily torpor (Ruf & Geiser, 2015). As there are currently no

studies on the effect of torpor on brain size, future research is needed to determine whether torpor is related to brain size in the same manner as hibernation.

In bats, the only mammals to have evolved true flight, a large proportion of species hibernates (around 28% in our dataset). Apart from the strategy of escaping in time by hibernation, bats use another strategy of dealing with seasonal food scarcity, escaping in space by migration. However, the expensive brain framework predicts that migration also comes at a cost for brain size evolution. High-intensity migratory flight demands a continuous supply of energy, which is expected to trade-off against brain size. Not surprisingly, migratory bats were found to have smaller brains than sedentary species (McGuire & Ratcliffe, 2011). Birds, the other group of flying vertebrates, do not hibernate but use migration to survive seasonally lean periods by switching habitats. As in bats, migratory bird species were also found to be relatively smaller-brained than non-migratory species, presumably because they might not be able to provide enough energy for a large brain during the strenuous migratory journey (Sol *et al.*, 2005; Vincze, 2016).

In sum, using one of the largest mammalian brain size dataset to date, we found that hibernators have significantly smaller brain sizes relative to body mass than non-hibernating species overall (species-level), and within five out of seven orders. This result adds to numerous previous studies supporting the idea that experienced seasonality (*in extremis* where hibernation is necessary for survival) imposes an energetic challenge, and thus acts as an evolutionary constraint on brain size (van Woerden *et al.*, 2010; Jiang *et al.*, 2015; Weisbecker *et al.*, 2015; Luo *et al.*, 2017; Veitschegger, 2017). This energetic challenge imposed by the environment also provides one explanation why ectothermic species such as reptiles, amphibians, fishes and insects do have smaller brain size relative to body mass compared to endothermic species such as mammals and birds, as previously pointed out by Gillooly and McCoy (2014). Ectothermic organisms rely on environmental heat sources

which allows them to operate at very economical metabolic rates. However, as a result ectothermic animals may not be able to hold the energy supply for a large brain constant. Similar to hibernating mammals, when the environmental temperature and hence also the body temperature of ectotherm organisms decreases, biochemical reaction rates and associated dynamics (e.g., heart rate) are also slowing down, which may ultimately act as a constraint on brain size.

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Figure and Table

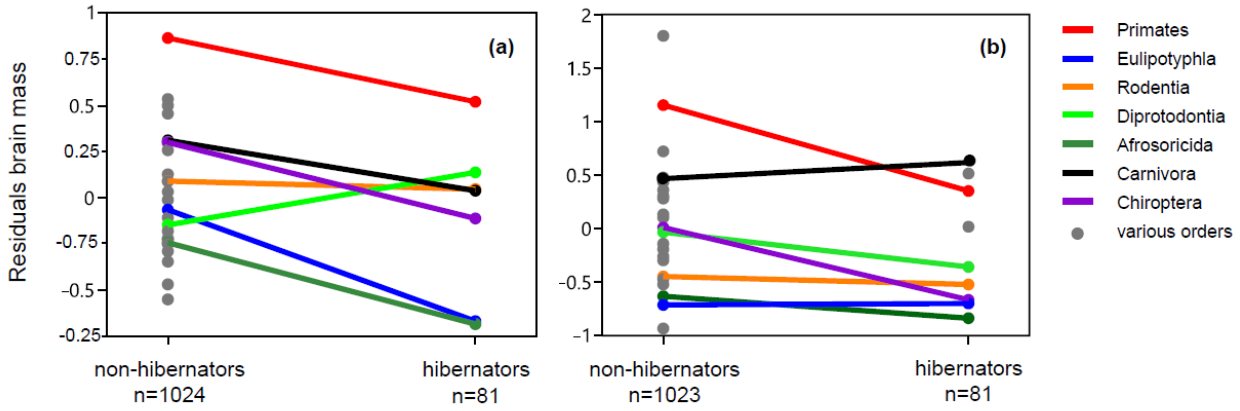

Fig. 1 Relative brain size (corrected for body mass) for hibernating versus non-hibernating species of mammalian orders. Presented are **(a)** raw non-phylogenetically corrected residuals and **(b)** raw non-phylogenetically corrected residuals, but with the slope of the regression line fixed to $\beta = 0.59017$ based on the phylogenetic corrected regression of brain vs. body mass . Thus, (b) is more closely matching the results of the phylogenetic generalized least-squares regression models shown in Table 2. As predicted by the expensive brain framework, hibernating species had relatively smaller brains compared to non-hibernating species, on both the species-level and within most orders (5 out of 7 orders that contain both hibernators and non-hibernators). Details of phylogenetic models are shown in Tables 1 and 2, species values are listed in Appendix S1. Note: The order Carnivora shows a positive trend in (b), although the phylogenetic generalized least squares analysis yields a significantly negative effect of hibernation on brain size (Table 2). This discrepancy arises from the fact that hibernating species occur mainly within relatively large-brained families of Carnivora, such as Ursidae or Canidae. Within these families, the direction of the effect of hibernation on brain size is also negative (Fig. S1).

Table 1 Phylogenetic generalized least squares models with brain size as response variable and hibernation, log(mean body mass), and covariates (diurnality, substrate use, diet and mid-latitude of geographical distribution) as explanatory variables. (full data set: λ=0.961, adj. r^2=0.881, $F_{2, 1101}$ = 4090 of the first model, λ=0.961, adj. r^2=0.881, $F_{6, 1092}$ = 1358 of the second model including covariates; data set excluding all mammalian orders without hibernators: λ=0.962, adj. r^2=0.881, $F_{2, 887}$ = 3292 of the first model, λ=0.961, adj. r^2=0.882, $F_{6, 868}$ = 1097 of the second model including covariates). The *P*-values of all four models were <0.001 Significant effects are highlighted in bold.

Predictor	**full data set**	Estimate	SE	*t*	*P*	**excluding orders without hibernators**	Estimate	SE	*t*	*P*
hibernation	n = 1104	-0.146	0.038	-3.849	**<0.001**	n = 890	-0.143	0.035	-4.048	**<0.001**
log (mean body mass)		0.589	0.007	89.943	**<0.001**		0.594	0.007	80.615	**<0.001**
hibernation	n = 1099	-0.143	0.038	-3.746	**<0.001**	n = 885	-0.141	0.035	-3.969	**<0.001**
log (mean body mass)		0.588	0.007	88.682	**<0.001**		0.596	0.007	79.780	**<0.001**
diurnality		0.036	0.021	1.741	0.082		0.030	0.023	1.304	0.193
substrate use		-0.013	0.016	-0.795	0.427		0.005	0.016	0.320	0.749
diet		0.002	0.011	0.146	0.884		0.012	0.011	1.125	0.261
latitude of geographical distribution		<-0.001	<0.001	-1.296	0.195		<-0.001	<0.001	-1.669	0.095

Table 2 Phylogenetic generalized least squares models within orders with brain size as response variable and hibernation and log(mean body mass) as explanatory variables. The *P*-values of all models were <0.001. Significant effects are highlighted in bold.

Order	*N*	λ	Adj. r^2	Predictor	Estimate	SE	*t*	*P*
Afrosoricida	11	0	0.947	hibernation	-0.363	0.120	-3.021	**0.017**
				log (mean body mass)	0.669	0.052	12.869	**<0.001**
Carnivora	183	0.819	0.882	hibernation	-0.198	0.090	-2.198	**0.029**
				log (mean body mass)	0.590	0.016	36.867	**<0.001**
Chiroptera	81	0.869	0.934	hibernation	-0.121	0.057	-2.146	**0.035**
				log (mean body mass)	0.654	0.020	32.280	**<0.001**
Diprotodontia	87	0.977	0.877	hibernation	-0.601	0.252	-2.386	**0.019**
				log (mean body mass)	0.516	0.024	21.856	**<0.001**
Eulipotyphla	34	0	0.948	hibernation	-0.319	0.204	-1.562	0.129
				log (mean body mass)	0.665	0.037	17.853	**<0.001**
Primates	205	0.960	0.828	hibernation	-0.057	0.122	-0.466	0.642
				log (mean body mass)	0.646	0.021	30.488	**<0.001**
Rodentia	287	0.831	0.909	hibernation	-0.101	0.052	-1.952	**0.050**
				log (mean body mass)	0.578	0.011	53.297	**<0.001**

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1 List of species and data used for this study

Figure S1 Relative brain size (corrected for body mass) for hibernating versus non-hibernating species within Carnivora families.

Tables S1 Phylogenetic generalized least-squared regressions within orders with brain size as response variable, and hibernation, log(mean body mass), and covariates (diurnality, substrate use, diet and mid-latitude of geographical distribution) as explanatory variables. Significant effects are highlighted in bold.